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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/851,628	05/06/97	COHEN	C CRP-145

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EXAMINER	
ROMEO, D	
ART UNIT	**PAPER NUMBER**
1646	18

DATE MAILED: 05/09/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/851,628	Cohen et al.
Examiner	**Group Art Unit**
David S. Romeo	1646

☒ Responsive to communication(s) filed on *11 Feb 2000*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-4, 6-10, 12, 15-17, 24, 28, and 32-34* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-4, 6-10, 12, 15-17, 24, 28, and 32-34* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. The request filed on 02/11/00 (Paper No. 16) for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08851628 is acceptable and a CPA has been established. An action on the CPA follows.

2. Claims 1-4, 6-10, 12, 15-17, 24, 28, 32-34 are pending and are being examined.

3. Any objection or rejection of record that is not maintained in this Office action is withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

New formal matters, objections, and/or rejections:

Claim Rejections - 35 USC § 112

4. Claims 1-4, 6-10, 12, 15-17, 24, 28, 32-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of a mammal at risk of chronic renal failure, does not reasonably provide enablement for the treatment of a mammal in chronic renal failure. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The treatment of chronic renal failure and the improvement of renal function

implies the reversal of chronic renal failure. However, Brenner (u18) teaches that renal injury of a more sustained nature is often not reversible (page 1274, column 2, first paragraph of Brenner). Carpenter (vv18) teaches that chronic renal failure is irreversible (page 1281, column 2, first paragraph of Carpenter). The specification contains no working examples of, and lacks guidance for, reversing chronic renal. In view of the breadth of the claims, the irreversible nature of chronic renal failure, and the limited amount of direction and working examples provided by the inventor, it would require undue experimentation for the skilled artisan to use the full scope of the claimed invention.

5. Claims 1-3, 6-10, 12, 15-17, 24, 28, 32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treatment comprising administering OP1, does not reasonably provide enablement for a method of treatment comprising administering a protein having the recited % homology or % identity to OP1 or the C-terminal seven cysteine domain thereof, or for a method of treatment comprising administering "OP2, ... , and NEURAL". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The specification provides a single example of the administration of OP1 to a nephrectomized animal, and based on structural similarity, the specification asserts that proteins having the recited % homology or % identity to OP1 or the C-

terminal seven cysteine domain thereof, or "OP2, ... , and NEURAL" would have a similar activity. The assertions that these disparate proteins would have a similar activity cannot be accepted in the absence of supporting evidence because the relevant literature teaches that individual members of the TGF-β superfamily, or a subgroup thereof, do not necessarily share the same biological activities. Vukicevic (ww18) teaches that OP-1 promotes cell condensations and tubulogenesis in metanephric mesenchyme but BMP-2, a closely related member of the TGF-β superfamily, and TGF-β1 had no effect (page 9023, paragraph bridging columns 1-2). Vukicevic establishes that closely related members of the TGF-β superfamily have unpredictable effects, or that their effects cannot be predicted based upon % homology or identity. In general, the art recognizes that function cannot be predicted on structural information alone. See Bowie (w6) page 1306, column 1, full paragraph 1, wherein it is taught that predicting structure, hence function, from primary amino acid sequence data is extremely complex, and it unlikely the problem will be solved in the near future. Ngo (xx18) teach that the native structure of a protein is a unique three-dimensional structure into which the protein folds under physiological conditions and all the information necessary to determine the native structure can be contained in the primary amino acid sequence (page 433, full paragraph 1). However, it is not even known whether there exist an efficient algorithm for predicting the structure of a given protein from its amino acid sequence alone (page 492, full paragraph 2). The instant specification has not told the skilled artisan how to use a renal therapeutic agent comprising a protein, wherein the protein has the

recited % homology or % identity to OP1 or the C-terminal seven cysteine domain thereof, or "OP2, ... , and NEURAL" and wherein the protein does not have renal therapeutic activity, and the instant specification has not told the skilled artisan how to make a renal therapeutic agent with a protein does not have renal therapeutic activity. In view of the breadth of the claims, the limited amount of direction and working examples provided by the inventor, and the unpredictability in the art, it would require undue experimentation for the skilled artisan to make and/or use the full scope of the claimed invention.

6. The following claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim(s) 1-4, 6-10, 15-17, 24, 28, 32 are indefinite because they recite the term "OP/BMP renal therapeutic agent". Because the instant specification does not identify that material element or combination of elements which is unique to, and, therefore, definitive of "OP/BMP renal therapeutic agent" an artisan cannot determine what additional limitations are placed upon a claim by the presence of this term. The specification defines renal therapeutic agents as certain proteins of eukaryotic origin (page 5, lines 14-15) and functional variants of polypeptides (page 5, line 19). It is unclear, for example, if the "amino acid sequence ... SEQ ID NO:1" or some other protein of eukaryotic origin, or component of the agent, is responsible for the therapeutic effect. The metes

and bounds of the claim(s) are not clearly set forth. It is suggested that the claims recite "polypeptide" instead of reciting "renal therapeutic agent".

Claims 1-4, 6-10, 12, 15-17, 24, 28, 32-34 are indefinite because they lack a process step which clearly relates back to the claim preamble and it is unclear what process is to be achieved; an intended use is not the same as achieving a result; in the absence of a recitation as to any treatment, or a process step producing a treatment, it is unclear what result of the treatment can be inferred. It is unclear if the treatment is synonymous with the improvement in renal function or if some other treatment is intended. The metes and bounds of the claim(s) are not clearly set forth. It is suggested that the preambles recite a method of improving renal function in a mammal at risk of chronic renal failure. Alternatively, if the specification provides the proper support it is suggested that the preambles recite a method of maintaining renal function in a mammal at risk of chronic renal failure.

Claims 6-10 recite the limitation "said protein". There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

7. Claims 1-4, 6-10, 12, 15-17, 24, 28, 32-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kuberasampath (BB, cited by Applicants) in view of Tolins (u18), Ponticelli

(v18), Klahr (w18), Watanabe (x18), Kees-Folts (y18), Glassock (v6), Brenner (u6), Coe (z18), Glassock (uu18).

The specification teaches that subjects that are kidney transplant recipients are subjects in, or at risks of, chronic renal failure (paragraph bridging pages 11-12). Kuberasampath teaches the administration of a morphogen, OP1, to a kidney transplant recipient (page 4, line 26; page 7, lines 29-33; page 12, line 30, through page 13, line 21). Kuberasampath teaches that damage to cells resulting from the effects of an inflammatory response by immune cell mediated tissue destruction has been implicated as the cause of reduced tissue function or loss of tissue function in the kidney; glomerulonephritis is believed to result in large part from unwanted acute inflammatory reactions and fibrosis (page 1, lines 21-33). The immune cell mediated tissue destruction often follows an initial tissue injury or insult; the secondary damage often is the source of significant tissue damage (page 2, lines 7-11). When the interruption of blood flow limits the oxygen supply to the proximal tubular cells of the kidney the cells may become irreversibly injured and the ensuing inflammatory responses to this initial injury provide additional insult to the affected tissue (page 3, full paragraph 1). The morphogen may be provided directly to the tissue (paragraph bridging pages 11-12). OP1 (page 14, line 30, through page 15, line 17) inhibits the adherence of LTB_4 activated PMN's to endothelium (Example 5, pages 74-75), inhibits cellular and humoral inflammatory reactions (Example 7, pages 78-80), and inhibits epithelial cell

proliferation (Example 10, page 86-87). Kuberasampath is silent with respect to the treatment of patients afflicted with the recited conditions and the improvement of renal function therein.

Tolins (u18) teaches that glomerular hypertension leads to progressive glomerular damage; early events are followed by inflammatory mechanisms; various therapeutic approaches can have beneficial effects despite their diverse mechanisms of action (Abstract); it is easy to predict that a wide variety of disparate therapeutic maneuvers may be effective in arresting or preventing glomerular injury (page 57G, column 1, last paragraph).

Ponticelli (v18) teaches that aggressive and prolonged treatment with corticosteroids and immunosuppressive agents may favor remission and may considerably improve the long-term prognosis in children with focal-segmental glomerulosclerosis (FSGS). Good results with prolonged corticotherapy have also been reported in adults. The renal prognosis is excellent in responders, suggesting a protective effect of therapy. See page S18, columns 1-2. The prolonged administration of corticosteroids carries the risks of severe and life threatening complications; there is growing evidence that immunosuppressive agents can favorable alter the course of disease (Abstract; page S19, column 2, full paragraph 1).

Klahr (w18) teaches that progressive glomerulosclerosis is typically associated with the infiltration of inflammatory cells and that it is now apparent that these cells may contribute to the progression of renal disease (paragraph bridging pages 1659-1660).

Watanabe (x18) teaches that neutrophilic polymorphonuclear leukocytes are important effector cells in glomerular diseases, including diabetic retinopathy (page 209, column 1, full paragraph 1).

Kees-Folts (y18) teaches that close examination of kidneys from patients with a variety of diagnoses has revealed the presence of invading leukocytes in the kidneys of patients with immune and non immune glomerulonephritides (page 366, paragraph bridging columns 1-2). Further, in experimental glomerulonephritides, abrogation of macrophage infiltration results in improved renal function (page 366, column 2, full paragraph 1).

Glassock (v6) teaches that monocytes (macrophages) are present in large numbers in the glomerulus and interstitium in many forms of glomerulonephritis and tubulointerstitial nephritis; interference with the accumulation of these cells within the kidney may ameliorate the clinical and morphological manifestations of the disease (paragraph bridging pages 1294-1295).

Brenner (u6) teaches that despite successful treatment of hypertension, urinary tract obstruction and infection, and systemic disease, many forms of renal injury progress inexorably to chronic renal failure (CRF) (page 1274, first paragraph of Brenner); those forms of glomerulonephritis that respond to immunosuppressive therapy should be treated aggressively (page 1281, column 1, full paragraph 1). Brenner also teaches that in the early stages of CRF GFR is reduced to levels about 35 to 50 percent of normal (page 1275, column 1, full paragraph 1). Diabetic nephropathy often leads to CRF. See Coe (z18), page 1252, Table 233-2. Coe also

teaches the detection of reduction in kidney size by ultrasonography or tomography (page 1253, column 2, full paragraph 2).

Tolins (u18), Ponticelli (v18), Klahr (w18), Watanabe (x18), Kees-Folts (y18), Glassock (v6), Brenner (u6), Coe (z18) do not teach the treatment of patients at risk of chronic renal failure with OP1. However, the inexorable progression of many forms of renal injury to CRF would suggest to one of ordinary skill in the art at the time of Applicants invention additional forms of treatment for patients at risk of CRF in addition to the successful treatment of hypertension, urinary tract obstruction and infection, and systemic disease. One of ordinary skill in the art would have a reasonable expectation that an additional form of treatment, such as anti-inflammatory therapy, would have a beneficial effect because glomerular hypertension leads to progressive glomerular damage; early events are followed by inflammatory mechanisms; various therapeutic approaches can have beneficial effects despite their diverse mechanisms of action; it is easy to predict that a wide variety of disparate therapeutic maneuvers may be effective in arresting or preventing glomerular injury. One of ordinary skill in the art would be motivated to use additional form of treatment because even if a form of therapy were found which only delayed the onset of end stage renal disease by five years in one out of ten patients with primary glomerular disease, it can be estimated on the basis of the current [1981] cost of maintenance dialysis that a savings of over 25 million dollars over that five year period would result. See Glassock (uu18), page 23, full paragraph 1. The success in using immunosuppressive therapy against

glomerulonephropathies provides a reasonable expectation that OP-1 would be effective in arresting glomerular injury. The risks of severe and life threatening complications associated with prolonged administration of corticosteroids provides motivation to use OP-1 for immunosuppressive therapy. One of ordinary skill in the art would reasonably expect that suppressing inflammation would reduce the infiltration of the capillaries by inflammatory cells and glomerular filtration rate would increase, or that suppressing inflammation would cause a clinically significant improvement in a standard marker of renal function, wherein said standard marker is glomerular filtration rate.

Applicants argue that a skilled artisan would not use anti-inflammatory therapy to treat CRF caused by non-immune, non-inflammatory conditions. Applicants' arguments have been fully considered but they are not persuasive.

There is no evidence of record that the conditions recited in claims 1 and 2 are non-immune, non-inflammatory conditions or that immune, inflammatory conditions in patients with such conditions do not play a role in the progression of renal disease, or that patients with such conditions would not respond to immunosuppressive therapy. To the contrary, Kuberasampath teaches that diabetes is a chronic inflammatory disease (page 13, lines 23, 24). Watanabe (x18) teaches that neutrophilic polymorphonuclear leukocytes are important effector cells in glomerular diseases, including diabetic retinopathy (page 209, column 1, full paragraph 1). Kees-Folts (y18) teaches that close examination of kidneys from patients with a variety of diagnoses has revealed

the presence of invading leukocytes in the kidneys of patients with immune and non immune glomerulonephritides (page 366, paragraph bridging columns 1-2). Further, in experimental glomerulonephritides, abrogation of macrophage infiltration results in improved renal function (page 366, column 2, full paragraph 1). Glassock (v18) teaches that monocytes (macrophages) are present in large numbers in the glomerulus and interstitium in many forms of glomerulonephritis and tubulointerstitial nephritis; interference with the accumulation of these cells within the kidney may ameliorate the clinical and morphological manifestations of the disease (paragraph bridging pages 1294-1295). In any case the claims do not require the treatment of such conditions. The claims only require the improvement in a standard marker of renal function. There is no indication that the one of ordinary skill in the art would not reasonably expect that anti-inflammatory therapies would lead to an improvement in a standard marker of renal function.

Double Patenting

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 1-4, 6-10, 12, 15-17, 24, 28, 32-34 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 8, 11-15, 19-22, 26, 34, 37, 46, 51-56 of copending Application No. 08643321. Although the conflicting claims are not identical, they are not patentably distinct from each other because each set of claims recites similar treatment methods using the same compounds administered to the same or similar patients for the same purpose. The end results of such treatments would naturally flow from the administration of such compounds.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

10. No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David S. Romeo whose telephone number is (703) 305-4050. The examiner can normally be reached on Monday through Friday from 6:45 a.m. to 3:15 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242.

Faxed draft or informal communications should be directed to the examiner at (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

David Romeo
DAVID ROMEO
PATENT EXAMINER
May 7, 2000